19. The method according to Claim 16 wherein 1 part by weight of cetrorelix acetate is dissolved in 100-1000 parts by weight of a 30% strength wt./wt. acetic acid, made up with water for injection so that a 3% strength wt./wt. aqueous acetic acid solution results, mixed with mannitol and made up with water for injection, then sterile-filtered, dispensed into injection vials and lyophilized.--

REMARKS

With entry of this amendment, claims 12-19 are under examination. Reconsideration is requested. Support for the newly entered claims can be found throughout the specification and in the originally filed claims. No new matter has been added.

Applicants affirm the election of Group I, claims 1-8 and 11 (now replaced by claims 12-19), with traverse. Applicants respectfully submit that the claims of Groups I-III are so linked as to form a single general inventive concept and that it would not be an undue burden for the Examiner to search all of the claims. Withdrawal of the restriction is respectfully requested.

Claims 1, 7 and 8 were rejected under 35 USC § 112, second paragraph as being indefinite. It is believed that the newly entered claims are not subject to this rejection, since they do not contain the language which the Examiner found to be unacceptable.

Claims 1 and 11 were rejected as being anticipated by Callahan et al., and claims 1-8 and 11 were rejected as being obvious over Callahan in view of EP 88 308573 (Finkenhauer) and further in view of Reissman et al., Moore, Yoshikawa et al., Brown et al., Stewart et al. or Kornreich et al. To the extent that these rejections may be considered to be applicable to the pending claims, they are traversed for the following reasons.

Callahan et al. (US 4,908,475) relates to new vasopressin compounds but not LHRH analogs such as cetrorelix. A method of preparation of the new compounds is also described. In order to purify the peptide, the compound was extracted with 120 ml of 10% HOAc and 120 ml of 1% HOAc. In this case only the peptide acetate was formed in an aqueous solution. The use of an aqueous acetic acid solution in order to dissolve the peptide salt to avoid gel formation is not described.

Reissmann et al. (Cancer Research and Clinical Oncology Vol. pp 44-49 No. 1 1992) only describe pharmacological results with cetrorelix trifluoroacetate and cetrorelix acetate utilized as bulk substance and not as a sterile lyophilisate. In addition a process of preparing a sterile cetrorelix lyphilisate is not described in this article.

Moore (US 4,711,877) relates to new cyclic peptides with a structure similar to vasopressin and not to LHRH analogs. After the peptide is eluted from a column with pyridine acetate buffer the residue is removed in vacuum and the

residue is lyophilized from 10% acetic acid. There is no description of how to prepare a sterile lyophilisate using a peptide which usually will change into the undesired and unfiltrable gel form.

Kornreich (4,701,499) teaches how an N-substituted peptide can conveniently be dissolved in diluted acetic acid and then lyophilized. Komreich does not describe how to make a sterile filtrate and lyophilisate from a gel forming peptide salt.

Yosikawa (US 5,268,360) describes opioid peptides received from hydrolysis of wheat proteins. The peptides were liberated from the resin, the solvent (hydrogen fluoride) was distilled off and the residue was extracted with 30% acetic acid and lyophilized. In this patent there is no part which shows difficulties caused by filtration process in order to produce a sterile final product.

Brown (US 4,372,884) describes peptide which inhibit the secretion of pituitary gland growth hormone. The peptide material was eluted from a Bio Rex-70 resin column with pyridine acetic acid water or 50% acetic acid. The fractions were diluted with water and lyophilized. There is no teaching how to prepare a filterable peptide solution using acetic acid.

If a person skilled in art were to use the method of Callehan et al. and the method of Finkenhauer with the addition of bulking agents, he would not achieve any success

in carrying out a sterile filtration of a peptide solution, particularly if the peptide shows gelling properties.

The purpose of the present invention is not only how to carry out a lyophilisation of certain peptides but more importantly how to produce a sterile lyophilisate of those compounds. In order to produce a sterile lyophilisate, a sterilization by filtration must be performed (see USP 23/NI-18 Pages 1650, 1997, 1978). This is not feasible with a solution of a gelling peptide unless acetic acid is used. Therefore a solution to the described problem of sterilization by filtration can not be achieved by combining the prior art teachings.

All rejections having been addressed, it is respectfully submitted that this application is in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

CUSHMAN DARBY & CUSHMAN
Intellectual Property Group of
Pillsbury Madison & Sutro, LLP

By _____
Ann S. Hobbs, Ph.D.
Reg. No. 36,830
Tel: (202) 861-3063

1100 New York Avenue
Ninth Floor
Washington, D.C. 20005